PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 50059/005W02 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US99/17738 | 06 AUGUST 1999 | 07 AUGUST 1998 |
| International Patent Classification (IPC) or national classification and IPC<br>IPC(7): G01N 33/53; C12N 15/86; C07H 21/04 and US Cl.: 435/7.1, 7.23, 325; 536/23.1 | | |
| Applicant<br>DANA-FARBER CANCER INSTITUTE | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 07 MARCH 2000 | 20 NOVEMBER 2000 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Kathrea Lawrence for<br>MINH TAM DAVIS<br>Telephone No. (703) 308-0196 |

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/17738

## I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-87 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 88-103 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1-37 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages 1-51 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 2-4,16-17,24-47,49,51,53-77,85

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. (See Attached).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | (Please See supplemental sheet) | YES |
| | Claims | (Please See supplemental sheet) | NO |
| Inventive Step (IS) | Claims | (Please See supplemental sheet) | YES |
| | Claims | (Please See supplemental sheet) | NO |
| Industrial Applicability (IA) | Claims | (Please See supplemental sheet) | YES |
| | Claims | (Please See supplemental sheet) | NO |

2. citations and explanations (Rule 70.7)

Claims 18,20-21,50,78, and 80-84 lack novelty under PCT Article 33(2) as being anticipated by Accession Nos: AI459806, AI590782,AI115047.

AI459806, AI590782,AI115047 teach nucleic acid sequences that are 99.5% similar to SEQ ID NO:1, 99.3% similar to SEQ ID NO:3, and 82.4% similar to SEQ ID NO:17, respectively. Thus the nucleic acid sequences taught by the prior art encode a polypeptide which is "substantially" identical to the polypeptide encoded by SEQ ID NO:1, 3 or 17. The DNA sequences taught by the prior art could also be a probe, the complementary sequence of which inherently would hybridize under high stringency conditions to TRAAM, wherein TRAAM comprises SEQ ID NO:1, 3, or 17. The DNA sequences taught by the prior art would encode a tumor antigen of any size, or a fragment of at least 10 amino acids, wherein said tumor antigen or fragment is encoded by TRAAM. The DNA sequences taught by the prior art would encode a polypeptide "substantially" identical to the polypeptide set forth in SEQ ID NO:18 or 19, wherein SEQ ID NO:18 or 19 is the polypeptide encoded by TRAAM nucleic acid sequences. The DNA sequences taught by AI459806, AI590782 comprise at least 14 or 16 consecutive nucleotides that are at least 85% similar to a TRAAM nucleotide, SEQ ID NO: 1 or 3, which encodes a TRAAM polypeptide, wherein the complementary sequence of said nucleotide sequence taught by the prior art inherently would hybridize under high stringency to a TRAAM nucleotide, SEQ ID NO: 1 or 3, which encodes a TRAAM polypeptide.

Claims 22, 23, and 52 lack an inventive step under PCT Article 33(3) as being obvious over AI459806, AI590782,AI115047. It would have been obvious to link the sequence taught by AI459806, AI590782,AI115047 to an expression vector, and to transform said vector in a host cell, because it is routine in the art to link a DNA sequence to an expression vector, and to transform said vector in a host cell.

Claims 1, 5-15 lack an inventive step under PCT Article 33(3) (Continued on Supplemental Sheet.)

**Supplemental B x**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



III. NON-ESTABLISHMENT OF REPORT:

No international search report has been established for claim numbers 2-4,16-17,24-47,49,51,53-77,85.

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 1, 5-15, 19, 22-23, 48, 52, 79.
The report as to Novelty was negative (NO) with respect to claims 18, 20-21, 50, 78, 80-84.
The report as to Inventive Step was positive (YES) with respect to claims 19, 48, 79.
The report as to Inventive Step was negative (NO) with respect to claims 1, 5-15, 18, 20-23, 50, 52, 78, 80-84 .
The report as to Industrial Applicability was positive (YES) with respect to claims 1, 5-15, 18-23, 48, 50, 52, 78-84.
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
as being obvious over Takahashi et al, in view of Dranoff et al. Takahashi et al teach that human cutaneous melanoma has been proven to be antigenic through analysis of patient sera, or peripheral blood lymphocytes (PBLs), and that this has led to the identification of many immunogenic tumor associated antigen (TAA) using antibodies or human CTLs cells (p.1363). In other words, PBLs of said patient or antibodies produced in said patient sera would recognize TAA. Dranoff et al teach that vaccination with irradiated tumor cells that are engineered to secrete granulocyte-macrophage colony-stimulating factor would increase anti-tumor immunity, as compared to administration of irradiated tumor alone. Therefore, it would have been obvious to identify TAA using the method taught by Takahashi et al, i.e. using antibodies from patient sera to identify TAA. It would have been obvious to combine the methods taught by Takahashi et al and Dranoff et al, because by logical reasoning, vaccination a patient with irradiated tumor cells that are engineered to secrete granulocyte-macrophage colony-stimulating factor would increase anti-tumor immunity, as taught by Dranoff et al, i.e. would enhance the potency of the antibodies in patient sera, and thus would increase the sensitivity of the method detection of TAA, using antibodies from patient sera, as taught by Takahashi et al.

---------- NEW CITATIONS ----------
NONE

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: CLARK T. PAUL
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MASSACHUSETTS 02110-2214

# PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| | |
|---|---|
| Date of Mailing *(day/month/year)* | 08 JAN 2001 |
| Applicant's or agent's file reference: 50059/005W02 | IMPORTANT NOTIFICATION |

| International application No. | International filing date *(day/month/year)* | Priority Date *(day/month/year)* |
|---|---|---|
| PCT/US99/17738 | 06 AUGUST 1999 | 07 AUGUST 1998 |

Applicant
DANA-FARBER CANCER INSTITUTE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/US | Authorized officer |
|---|---|
| Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | MINH TAM DAVIS<br>Dorothea Lawrence for |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

Form PCT/IPEA/416 (July 1992)★

TENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>50059/005W02 | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No.<br>PCT/US99/17738 | International filing date *(day/month/year)*<br>06 AUGUST 1999 | Priority date *(day/month/year)*<br>07 AUGUST 1998 |
| International Patent Classification (IPC) or national classification and IPC<br>IPC(7): G01N 33/53; C12N 15/86; C07H 21/04 and US Cl.: 435/7.1, 7.23, 325; 536/23.1 | | |
| Applicant<br>DANA-FARBER CANCER INSTITUTE | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand<br>07 MARCH 2000 | Date of completion of this report<br>20 NOVEMBER 2000 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Dorthea Lawrence for<br>MINH TAM DAVIS<br>Telephone No. (703) 308-0196 |

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/17738

## I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-87, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the claims:
pages 88-103, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the drawings:
pages 1-37, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the sequence listing part of the description:
pages 1-51, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language ____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

**III. N n- stablishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 2-4,16-17,24-47,49,51,53-77,85

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. (See Attached) .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reas ned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citati ns and explanations supporting such statement**

1. statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | (Please See supplemental sheet) | YES |
| | Claims | (Please See supplemental sheet) | NO |
| Inventive Step (IS) | Claims | (Please See supplemental sheet) | YES |
| | Claims | (Please See supplemental sheet) | NO |
| Industrial Applicability (IA) | Claims | (Please See supplemental sheet) | YES |
| | Claims | (Please See supplemental sheet) | NO |

2. citations and explanations (Rule 70.7)

Claims 18,20-21,50,78, and 80-84 lack novelty under PCT Article 33(2) as being anticipated by Accession Nos: AI459806, AI590782,AI115047.

AI459806, AI590782,AI115047 teach nucleic acid sequences that are 99.5% similar to SEQ ID NO:1, 99.3% similar to SEQ ID NO:3, and 82.4% similar to SEQ ID NO:17, respectively. Thus the nucleic acid sequences taught by the prior art encode a polypeptide which is "substantially" identical to the polypeptide encoded by SEQ ID NO:1, 3 or 17. The DNA sequences taught by the prior art could also be a probe, the complementary sequence of which inherently would hybridize under high stringency conditions to TRAAM, wherein TRAAM comprises SEQ ID NO:1, 3, or 17. The DNA sequences taught by the prior art would encode a tumor antigen of any size, or a fragment of at least 10 amino acids, wherein said tumor antigen or fragment is encoded by TRAAM. The DNA sequences taught by the prior art would encode a polypeptide "substantially" identical to the polypeptide set forth in SEQ ID NO:18 or 19, wherein SEQ ID NO:18 or 19 is the polypeptide encoded by TRAAM nucleic acid sequences. The DNA sequences taught by AI459806, AI590782 comprise at least 14 or 16 consecutive nucleotides that are at least 85% similar to a TRAAM nucleotide, SEQ ID NO: 1 or 3, which encodes a TRAAM polypeptide, wherein the complementary sequence of said nucleotide sequence taught by the prior art inherently would hybridize under high stringency to a TRAAM nucleotide, SEQ ID NO: 1 or 3, which encodes a TRAAM polypeptide.

Claims 22, 23, and 52 lack an inventive step under PCT Article 33(3) as being obvious over AI459806, AI590782,AI115047. It would have been obvious to link the sequence taught by AI459806, AI590782,AI115047 to an expression vector, and to transform said vector in a host cell, because it is routine in the art to link a DNA sequence to an expression vector, and to transform said vector in a host cell.

Claims 1, 5-15 lack an inventive step under PCT Article 33(3) (Continued on Supplemental Sheet.)

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)



Continuation of: Boxes I - VIII

III. NON-ESTABLISHMENT OF REPORT:

No international search report has been established for claim numbers 2-4,16-17,24-47,49,51,53-77,85.

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 1, 5-15, 19, 22-23, 48, 52, 79.
The report as to Novelty was negative (NO) with respect to claims 18, 20-21, 50, 78, 80-84.
The report as to Inventive Step was positive (YES) with respect to claims 19, 48, 79.
The report as to Inventive Step was negative (NO) with respect to claims 1, 5-15, 18, 20-23, 50, 52, 78, 80-84 .
The report as to Industrial Applicability was positive (YES) with respect to claims 1, 5-15, 18-23, 48, 50, 52, 78-84.
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
as being obvious over Takahashi et al, in view of Dranoff et al. Takahashi et al teach that human cutaneous melanoma has been proven to be antigenic through analysis of patient sera, or peripheral blood lymphocytes (PBLs), and that this has led to the identification of many immunogenic tumor associated antigen (TAA) using antibodies or human CTLs cells (p.1363). In other words, PBLs of said patient or antibodies produced in said patient sera would recognize TAA. Dranoff et al teach that vaccination with irradiated tumor cells that are engineered to secrete granulocyte-macrophage colony-stimulating factor would increase anti-tumor immunity, as compared to administration of irradiated tumor alone. Therefore, it would have been obvious to identify TAA using the method taught by Takahashi et al, i.e. using antibodies from patient sera to identify TAA. It would have been obvious to combine the methods taught by Takahashi et al and Dranoff et al, because by logical reasoning, vaccination a patient with irradiated tumor cells that are engineered to secrete granulocyte-macrophage colony-stimulating factor would increase anti-tumor immunity, as taught by Dranoff et al, i.e. would enhance the potency of the antibodies in patient sera, and thus would increase the sensitivity of the method detection of TAA, using antibodies from patient sera, as taught by Takahashi et al.

---------- NEW CITATIONS ----------
NONE

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: CLARK T. PAUL
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MASSACHUSETTS 02110-2214

# PCT

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

**(PCT Rule 44.1)**

| | |
|---|---|
| | Date of Mailing *(day/month/year)* 08 FEB 2000 |
| Applicant's or agent's file reference 50059/005W02 | **FOR FURTHER ACTION** **See paragraphs 1 and 4 below** |
| International application No. PCT/US99/17738 | International filing date *(day/month/year)* 06 AUGUST 1999 |
| Applicant DANA-FARBER CANCER INSTITUTE | |

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

**For more detailed instructions,** see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

| | |
|---|---|
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>MINH-TAM DAVIS |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

Form PCT/ISA/220 (January 1994)★ *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>50059/005W02 | **FOR FURTHER ACTION** | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No.<br>PCT/US99/17738 | International filing date *(day/month/year)*<br>06 AUGUST 1999 | (Earliest) Priority Date *(day/month/year)*<br>07 AUGUST 1998 |
| Applicant<br>DANA-FARBER CANCER INSTITUTE | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 10 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [X] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17738

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 5-15, 18-23, 48, 50, 52, 55-61, 78-84

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17738

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :435/7.1, 7.23, 325; 536/23.1
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 7.23, 325; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MPSRCH, DIALOG, WEST
search terms: antibody, antigen, tumor, GM-CSF, cytokines

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | TAKAHASHI et al. 707-AP peptide recognized by human antibody induces human leukocyte antigen A2-restricted cytotoxic T lymphocyte killing of melanoma. Clin. Cancer Res. August 1997, Vol. 3, pages 1363-1370, see entire document. | 1, 14-15 |
| Y | DRANOFF et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony- stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc. Natl. Acad. Sci. USA. April 1993, Vol. 90, pages 3539-3543, see entire document. | 1, 5-13 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search
05 JANUARY 2000

Date of mailing of the international search report
08 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
MINH-TAM DAVIS

Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17738

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y,P | JAGER et al. Strategies for the development of vaccines to treat breast cancer. Recent Results Cancer Res (Germany). 1998, Vol. 152, pages 94-102, see entire document. | 1, 5-13 |
| X - Y | Database Genbank, Accession No. AI459806, Hillier et al. WashU-NCI human EST Project. Unpublished 1997, 09 March 1999, see entire document. | 18, 20, 21, 50, 78, 80-84 ---------- 22, 23, 52 |
| X - Y | Database Genbank, Accession No. AI590782, NCI-CGAP http://ww.ncbi.nih.gov/ncicgap. National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index. Unpublished 1997, 14 May 1999, see entire document. | 18, 20-21, 50, 78, 80-84 ---------- 22, 23, 52 |
| X - Y | Database Genbank, Accession No. AI115047, Marra et al., The WashU-HHMI Mouse EST Project. Unpublished 1996, 02 September 1998, see entire document. | 18, 20, 21, 50, 78, 80- 84 ---------- 22, 23, 52 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17738

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

G01N 33/53; C12N 15/86; C07H 21/04

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.
Group I, claim(s) 1, 5-15, 18-23, 48, 50, 52, 55-61, 78-84, drawn to 1) a method of identifying a nucleic acid encoding a tumor antigen, using an antibody, 2) a method for diagnosing a tumor, by detecting an antibody that specifically binds to a tumor antigen, 3) a nucleic acid sequence encoding a tumor antigen, its fragments, and a vaccine comprising said nucleic acid sequence.
Group II, claim(s) 2, 5-13, drawn to a method of identifying a nucleic acid encoding a tumor antigen, using cytotoxic T lymphocytes.
Group III, claim(s) 3, 5-13, 24, 25, 26, 27, 29, 38, drawn to an antibody to a tumor antigen, a method for detecting the presence of a tumor or tumor antigen, using said antibody, and a method for detecting the level of said antibody in a patient.
Group IV, claim(s) 4, 5-13, drawn to a method of identifying a tumor antigen, using cytotoxic T lymphocytes.
Group V, claim(s) 14-15, 30, 31, 36, 37, drawn to a method diagnosing a tumor, by detecting a tumor antigen.
Group VI, claim(s) claims 14-15, 30, 32-37, drawn to a method for diagnosing a tumor, by detecting a nucleic acid sequence encoding a tumor antigen.
Group VII, claim(s) 14-15, 28-29, drawn to a method for diagnosing a tumor, by detecting cytotoxic T lymphocytes that specifically bind to a tumor antigen.
Group VIII, claim(s) 16, 17, 49, 53, 54, 74-77, drawn to a tumor antigen polypeptide, or a fragment thereof, and a vaccine comprising a tumor antigen polypeptide, or a fragment thereof.
Group IX, claim(s) 39, 40, drawn to a method treatment or prophylaxis of a tumor by vaccinating with a tumor antigen polypeptide.
Group X, claim(s) 39, 41-45, 51, drawn to a method of treatment or prophylaxis of a tumor by vaccinating with nucleic acid sequence encoding a tumor antigen.
Group XI, claim(s) 46, 47, drawn to a method of treatment of a tumor by administering an antibody.
Group XII, claim 62, drawn to an antisense MAIAP nucleic acid.
Group XIII, claim(s) 63-66, drawn to a method for stimulating apoptosis.
Group XIV, claim(s) 67-70, drawn to a method for inhibiting apoptosis.
Group XV, claim(s) claims 71-73, drawn to a method for identifying a compound that modulates apoptosis or radiation sensitivity.
Group XVI, claim 85, drawn to an antisense TRAAM nucleic acid.

This application contains claims directed to more than one subgroup of the generic invention. These subgroups are deemed to lack Unity of Invention because they are not so linked as to forma single inventive concept under PCT Rule 13.1. In order for more than one subgroups to be searched, the appropriate additional search fees must be paid.

The subgroups from any of groups I-X1 are as follows: the polypeptides TRAAM, TPR/UBP3, UBP3, BRAP-2/H-ATPase, K008-1, MAIAP, Gene AS, BR-1, or BR-2, or the nucleotide sequences encoding said polypeptides.

The subgroups from any of groups IX-X are as follows: treatment or prophylaxis.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species from any of groups I-XVI are as follows: leukemia, lymphoma, brain tumor, melanoma, fibrosarcoma, carcinoma of uterine, cervical, testicular, liver, ovarian, lung, renal cell, colon, breast, prostate, or bladder.

and it considers that the Internation Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-XVI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special features for the following reasons:

An international stage application shall relate to one invention only or to a group of invention so linked as to form a

single general inventive concept if multiple products, processes of manufacture of uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3)(a) and 1.476(c), 37 C.F.R. 1.475(d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).

Group I, claims 1, 5-15, 18-23, 48, 50, 52, 55-61, 78-84 form a single inventive concept, i.e. a nucleic acid sequence encoding a tumor antigen, and the first methods of how to make and use said nucleic acid sequence. Groups III, VIII, XII, and XVI are additional products, i.e. an antibody against a tumor antigen polypeptide, a tumor antigen polypeptide, and an antisense of a nucleic acid sequence encoding a tumor antigen polypeptide. All of said products are functionally and/or structurally different from the nucleic acid sequence of group I. The methods of groups II-VII, IX-XI, XIII-XV are additional methods, which are different from the methods of group I, and from each other by different objectives and/or using different means.
The species are distinct from each other because they are different types of cancer, having different etiology and/or from different origin.

RECORD COPY

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/US 99/17738
International Application No.

(06.08.99) 06 AUG 1999
International Filing Date

[redacted]
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) 50059/005W02

**Box No. I TITLE OF INVENTION**

TUMOR ANTIGENS AND USES THEREOF

**Box No. II APPLICANT**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Change See #12

DANA-FARBER CANCER INSTITUTE
44 Binney Street
Boston, Massachusetts 02115
United States of America

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DRANOFF, Glenn
25 OUTLOOK DRIVE
LEXINGTON, MA 02142 US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CLARK, Paul T.
Clark & Elbing LLP
176 Federal Street
Boston, Massachusetts 02110-2214
United States of America

Telephone No.
(617) 428-0200

Facsimile No.
(617) 428-7045

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. 2

**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

***If none of the following sub-boxes is used, this sheet should not be included in the request.***

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SCHMOLLINGER, JAN
98 CYPRESS ST #3
BROOKLINE, MA 02445 US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: ~~USA~~ US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HODI, F. STEPHEN
41 AUBURN ST #4
BROOKLINE, MA 02446 US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ~~USA~~ US

State *(that is, country)* of residence: ~~USA~~ US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MOLLICK, JOSEPH
42 EIGHTH ST # 5204
CHARLESTOWN, MA 02129 US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ~~USA~~ US

State *(that is, country)* of residence: ~~USA~~ US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

**Regional Patent**

- ☐ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

**National Patent** *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☐ **AL** Albania
- ☐ **AM** Armenia
- ☐ **AT** Austria
- ☒ **AU** Australia
- ☐ **AZ** Azerbaijan
- ☐ **BA** Bosnia and Herzegovina
- ☐ **BB** Barbados
- ☐ **BG** Bulgaria
- ☐ **BR** Brazil
- ☐ **BY** Belarus
- ☒ **CA** Canada
- ☐ **CH and LI** Switzerland and Liechtenstein
- ☐ **CN** China
- ☐ **CU** Cuba
- ☐ **CZ** Czech Republic
- ☐ **DE** Germany
- ☐ **DK** Denmark
- ☐ **EE** Estonia
- ☐ **ES** Spain
- ☐ **FI** Finland
- ☐ **GB** United Kingdom
- ☐ **GD** Grenada
- ☐ **GE** Georgia
- ☐ **GH** Ghana
- ☐ **GM** Gambia
- ☐ **HR** Croatia
- ☐ **HU** Hungary
- ☐ **ID** Indonesia
- ☐ **IL** Israel
- ☐ **IN** India
- ☐ **IS** Iceland
- ☒ **JP** Japan
- ☐ **KE** Kenya
- ☐ **KG** Kyrgyzstan
- ☐ **KP** Democratic People's Republic of Korea .....
- ☐ **KR** Republic of Korea
- ☐ **KZ** Kazakhstan
- ☐ **LC** Saint Lucia
- ☐ **LK** Sri Lanka
- ☐ **LR** Liberia
- ☐ **LS** Lesotho
- ☐ **LT** Lithuania
- ☐ **LU** Luxembourg
- ☐ **LV** Latvia
- ☐ **MD** Republic of Moldova
- ☐ **MG** Madagascar
- ☐ **MK** The former Yugoslav Republic of Macedonia .....
- ☐ **MN** Mongolia
- ☐ **MW** Malawi
- ☐ **MX** Mexico
- ☐ **NO** Norway
- ☐ **NZ** New Zealand
- ☐ **PL** Poland
- ☐ **PT** Portugal
- ☐ **RO** Romania
- ☐ **RU** Russian Federation
- ☐ **SD** Sudan
- ☐ **SE** Sweden
- ☐ **SG** Singapore
- ☐ **SI** Slovenia
- ☐ **SK** Slovakia
- ☐ **SL** Sierra Leone
- ☐ **TJ** Tajikistan
- ☐ **TM** Turkmenistan
- ☐ **TR** Turkey
- ☐ **TT** Trinidad and Tobago
- ☐ **UA** Ukraine
- ☐ **UG** Uganda
- ☒ **US** United States of America
  continuation-in-part
- ☐ **UZ** Uzbekistan
- ☐ **VN** Viet Nam
- ☐ **YU** Yugoslavia
- ☐ **ZW** Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....
- ☐ .....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being exclude from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

WITHDRAWN BY APPLICANT

**Supplemental Box** *If the Supplemental Box is not used, this sheet should not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "**patent of addition**," or "**certificate of addition**," or if, in Box No. V, the name of the United States of America is accompanied by an indication "**continuation**" or "**continuation-in-part**": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box No. V:

US: 60/095,766 Filed 07 August 1998 (07.08.98)

Sheet No. 5

**Box No. VI PRIORITY CLAIM** ☐ Further priority claims are indicated in the Supplemental Box.

| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: national application: country | regional application:* regional Office | international application: receiving Office |
|---|---|---|---|---|
| item (1) (07.08.98) 07 August 1998 | 60/095,766 | US | | |
| item (2) | | | | |
| item (3) | | | | |

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)** *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA / US

**Request to use results of earlier search; reference to that search** *(if an earlier search has been carried out by or requested from the International Searching Authority)*: Date *(day·month·year)* Number Country *(or regional Office)*

**Box No. VIII CHECK LIST; LANGUAGE OF FILING**

This international application contains the following **number of sheets**:

| | |
|---|---|
| request | 5 |
| description (excluding sequence listing part) | 87 |
| claims | 16 |
| abstract | 1 |
| drawings | 37 |
| sequence listing part of description | 5i |
| **Total number of sheets** | ~~198~~ 147 |

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Transmittal Letter

**Figure of the drawings** which should accompany the abstract:

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